

## PATENT COOPERATION TREATY

USA

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>x-12553</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 99/ 27801</b>	International filing date ( <i>day/month/year</i> ) <b>23/11/1999</b>	(Earliest) Priority Date ( <i>day/month/year</i> ) <b>30/11/1998</b>
Applicant <b>ELI LILLY AND COMPANY et al</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of **7** sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(e)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
  - contained in the international application in written form.
  - filed together with the international application in computer readable form.
  - furnished subsequently to this Authority in written form.
  - furnished subsequently to this Authority in computer readable form.
  - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  Certain claims were found unsearchable (See Box I).

3.  Unity of Invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.  
US 99/27801

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**Although claim 29 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
**see FURTHER INFORMATION sheet PCT/ISA/210**
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
**Claims 3, 17 completely, Claims 1, 2, 6-16, 18-32 partially.**

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box I.2

Claims 1-3,14,16-23,32 relate in part to a generic "NGE", without clearly specifying what this actually means. For the purpose of the search, it has been assumed, in the light of Table I and of the definition given on page 12, lines 7-17, that NGE represents a non-glycosylated form of the wild type erythropoietin sequence (e.g., expressed in non-glycosylating cells).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: (3,17) - completely; (1,2,6-16,18-32) - partly

A non-glycosylated erythropoietin (NGE) polypeptide selected from:

NGE,  
NGE-166del,  
MR-NGE,  
MR-NGE-166del.

Corresponding nucleic acids, vectors, host cells, transgenic animals, production methods.

Corresponding erythropoietic compound comprising said NGE and a polymer portion, wherein the polymer portion consists of 1 to 5 chains of formula [R-0-(CH<sub>2</sub>CH<sub>2</sub>-O)<sub>x</sub>-(CH<sub>2</sub>)<sub>y</sub>-NH], wherein R is H or C1 to C4 alkyl, x is a number from about 70 to 1200, and y is a number from 1 to 4, and the polymer chain is covalently bonded to the protein portion by a secondary amine; and a process for preparing said compound.

2. Claims: (1,2,6-16,18-32) - partly

Idem as subject-matter 1, but wherein the erythropoietin is a non-glycosylated erythropoietin (NGE) analog polypeptide selected from:

NGE-5E,  
NGE-5E-166del,  
MR-NGE-5E,  
MR-NGE-5E-166del  
MR-NGE-88E/K/P/S,  
MR-NGE-88E/K/P/S-166del  
MR-NGE-4E,  
MR-NGE-4E-166del

3. Claims: (4,5) - completely; (1,2,6-16,18-32) - partly

Idem as subject-matter 1, but wherein the erythropoietin is a non-glycosylated erythropoietin (NGE) analog polypeptide selected from:

NGE-W5E,  
NGE-W5E-166del,  
MR-NGE-W5K  
MR-NGE-W5K-166del

4. Claims: (6-11,15,24-32) - partly

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

As far as not covered by inventions 1-3:

An erythropoietic compound comprising a non-glycosylated human erythropoietin (or a non-glycosylated erythropoietin analog) and a polymer portion, wherein the polymer portion consists of 1 to 5 chains of formula [R-O-(CH<sub>2</sub>CH<sub>2</sub>-O)<sub>x</sub>-(CH<sub>2</sub>)<sub>y</sub>-NH], wherein R is H or C1 to C4 alkyl, x is a number from about 70 to 1200, and y is a number from 1 to 4, and the polymer chain is covalently bonded to the protein portion by a secondary amine; and a process for preparing said compound.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/27801

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 C12N15/12 C12K 21  
 A01K67/027 A61P7/06

C07K14/505

A61K47/48

A61K38/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WASLEY L.C. ET AL.: "The importance of N-and O-linked oligosaccharides for the biosynthesis and in vitro and in vivo biologic activities of erythropoietin" BLOOD, vol. 77, no. 12, 15 June 1991 (1991-06-15), pages 2624-2632, XP000907435 the whole document ---	1-3,14, 16-23,32
X	WO 91 05867 A (AMGEN INC) 2 May 1991 (1991-05-02) figure 8 ---	1-3,14, 16-23,32

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## ° Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

26 May 2000

Date of mailing of the international search report

05.09.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Galli, I

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/27801

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRANCIS G.E. ET AL.: "PEGylation of cytokines and other therapeutic proteins and peptides: the importance of biological optimisation of coupling techniques" INT. J. HEMATOL., vol. 68, no. 1, July 1998 (1998-07), pages 1-18, XP000907109 cited in the application the whole document figure 7 ---	6-11,15, 24-31
A	WO 98 32466 A (FRANCIS GILLIAN ELIZABETH ;FISHER DEREK (GB); MALIK FAROOQ (GB); P) 30 July 1998 (1998-07-30) abstract page 1 -page 5 example 8 ---	1-3,6-32
A	DUBE S ET AL: "GLYCOSYLATION AT SPECIFIC SITES OF ERYTHROPOIETIN IS ESSENTIAL FOR BIOSYNTHESIS, SECRETION, AND BIOLOGICAL FUNCTION" JOURNAL OF BIOLOGICAL CHEMISTRY, US, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vcl. 263, no. 33, 25 November 1988 (1988-11-25), pages 17516-17521, XP002053702 ISSN: 0021-9258 the whole document ---	1-3,6-32
A	WO 96 11953 A (AMGEN INC) 25 April 1996 (1996-04-25) example 2 claims 1,3-6,12,15-17 ---	24-28
A	WO 94 25055 A (ABBOTT LAB ;OKASINSKI GREGORY F (US); DEVRIES PETER J (US); MELLOV) 10 November 1994 (1994-11-10) abstract -----	1-3,6-32

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/27801

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9105867	A 02-05-1991	AT 146187 T AT 184914 T AU 646822 B AU 6604290 A CA 2027635 A CA 2165694 A CN 1051936 A DE 69029370 D DE 69029370 T DE 69033301 D DE 69033301 T DK 428267 T EP 0428267 A EP 0668351 A ES 2097753 T ES 2139764 T FI 964648 A GR 3022658 T HK 1006718 A JP 8151398 A JP 2983629 B JP 4502331 T NO 301832 B NZ 235676 A PT 95586 A,B US 5856298 A ZA 9008166 A		15-12-1996 15-10-1999 10-03-1994 16-05-1991 14-04-1991 14-04-1991 05-06-1991 23-01-1997 05-06-1997 28-10-1999 20-04-2000 09-06-1997 22-05-1991 23-08-1995 16-04-1997 16-02-2000 21-11-1996 31-05-1997 12-03-1999 11-06-1996 29-11-1999 23-04-1992 15-12-1997 28-04-1992 30-09-1991 05-01-1999 28-08-1991
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WO 9425055	A 10-11-1994	AU 697453 B AU 6778594 A BR 9406490 A CN 1125401 A CZ 9502844 A EP 0744953 A FI 955128 A		08-10-1998 21-11-1994 05-03-1996 26-06-1996 14-02-1996 04-12-1996 27-10-1995

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9425055	A	HU 73876 A	28-10-1996
		JP 8509614 T	15-10-1996
		NO 954342 A	30-10-1995
		US 5888772 A	30-03-1999